March 21, 2002

Edwin L. Mongan III
E.I. du Pont de Nemours & Company, Inc.
1007 Market Street
Wilmington, DE 19898

Dear Mr. Mongan:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 4,4'-Oxydianiline, posted on the ChemRTK HPV Challenge Program Web site on October 5, 2001. I commend DuPont for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its HPV Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that DuPont advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@.epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
4,4'-Oxydianiline

SUMMARY OF EPA COMMENTS

The sponsor, E.I. du Pont de Nemours & Co., Inc., submitted a Test Plan and Robust Summaries to EPA dated September 26, 2001, for 4,4'-oxydianiline (CAS Number 101-80-4). EPA posted the submission on the ChemRTK HPV Challenge Web site on October 5, 2001.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical and Environmental Fate Data.

The submitter needs to provide measured data for solubility in water (See Test Plan comments below). The planned biodegradation test should follow OECD Guideline 301 for ready biodegradability.

2. Health Effects. EPA agrees with the submitter's test plan that a developmental toxicity study is needed to address this endpoint.

3. Ecological Effects. The acute fish study was of insufficient duration, and the submitter needs to address this endpoint. Since only an ECOSAR prediction was provided to assess algal toxicity, the submitter needs to address this endpoint further. The supplied ECOSAR predictions alone cannot be used to support the existing data in the case of the fish endpoint, nor used in the absence of test data for the algae endpoint, to determine the toxicity of this chemical. The submitter needs to provide adequate measured data on related chemicals for these endpoints to support the predicted data.

EPA requests that the Submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE 4,4'- OXYDIANILINE CHALLENGE SUBMISSION

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The submitted data for melting point, boiling point, vapor pressure, and partition coefficient of 4,4'-oxydianiline are adequate for the purposes of the HPV Challenge program.

Water Solubility. The submitter needs to provide measured data for solubility in water. Having accurate water solubility data is important when addressing ecotoxicological endpoints. Furthermore, in general, EPA prefers measured data unless precluded by experimental obstacles. The use of estimated values introduces uncertainties that then become magnified in modeling applications.

Environmental Fate (Photodegradation, Stability in Water, Biodegradation, Fugacity).

The submitted data for the photodegradation, stability in water, and fugacity of 4,4'-oxydianiline are adequate for the purposes of the HPV Challenge program.

Biodegradation. The submitter indicates in its Test Plan (page 1) that insufficient data are available to assess the relative importance of biodegradation. EPA understands by this statement that the submitter

will provide biodegradation data for this chemical. The submitter should perform the biodegradation test following OECD Guideline 301, which tests for ready biodegradability.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Although EPA agrees that the endpoints for acute, repeated dose, genetic and reproductive toxicity have been addressed by the available data, the submitter needs to provide critical information in the robust summaries to assess their adequacy. EPA agrees with the submitter's test plan that testing is needed for developmental toxicity.

Repeated Dose Toxicity. The submitter has adequately addressed this endpoint by providing two robust summaries for 2-year feeding studies in rats and mice that include information on long-term effects of repeated dietary exposure of 4,4'-oxydianiline.

Developmental Toxicity. The submitter needs to state in the test plan which test guideline and route of exposure will be used for the proposed testing.

Ecological Effects (fish, daphnia, and algal toxicity).

Fish/Algae. The fish study duration of 24 hours is shorter than the required 96 hours for assessing the acute toxicity of 4,4'-oxydianiline (see specific comments on robust summaries.). An ECOSAR prediction alone cannot be used to support the existing 24-hour fish toxicity study, nor used in the absence of test data for the algae endpoint, to determine the toxicity of this chemical. The submitter needs to provide adequate measured data on related chemicals for these endpoints to support the predicted data. For more information on these topics see "Guidance on Developing Robust Summaries" and "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program" at http://www.epa.gov/opptintr/chemrtk/guidocs.htm and further guidance at http://www1.oecd.org/ehs/guide/index.htm.

Invertebrates. The submitted data for aquatic toxicity to invertebrates are adequate for the purposes of the HPV Challenge program.

Specific Comments on Robust Summaries

The submitter needs to add a "Remarks" section to the robust summaries in which the data from the additional references listed can be presented and discussed in the context of the main study.

Environmental Fate

Fugacity. The sponsor's treatment of transport (fugacity) is adequate, except that the sponsor needs to provide half-life data inputs to the model.

Health Effects

Acute Toxicity. In the ALD acute oral study, the submitter needs to report death rates at each dose. In the summary of the other oral LD_{50} study, the submitter needs to report the strain of rat and the standard deviation for the rat LD_{50}. In addition, EPA recommends that an LD_{50} value for mice which was reported in the NCI citation for the repeat dose toxicity robust summaries be included in the remarks section to strengthen this endpoint.

Repeat Dose Toxicity. The submitter needs to provide data for non-neoplastic lesions and data on histopathology in the robust summaries of both 2-year feeding studies.

Genetic Toxicity. The submitter needs to add the following information where available:

> *Reverse mutation in Salmonella typhimurium*. The number of mutants for each concentration and strain of Salmonella tested.
>
> *Chromosomal aberration in Chinese hamster ovary cells.* The number and type of chromosomal aberrations per metaphase and per chromosome, if such data are available.
>
> *In vivo micronucleus test in mice.* The effects (mitotic index, micronucleus frequency, or clinical signs) observed at each dose level and time period examined.

Reproductive Toxicity. The robust summary needs to clearly state levels (NOAEL/LOAEL) for both maternal and offspring toxicity.

Ecological Effects.

Fish and Algae. The robust summary provided for fish did not follow a standard guideline and reported a non-standard endpoint (24-hour toxicity).

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.